
Placebo-Controlled Trials in Psychiatric Research: An Ethical Perspective

Franklin G. Miller

The placebo-controlled trial is widely regarded as the gold standard for testing the efficacy of new treatments; however, this research design is subject to ethical controversy, especially when standard treatments of proven efficacy exist. After examining regulatory standards and ethical codes relevant to placebo-controlled trials, I offer a critique of arguments against the use of placebo control groups in psychiatric research. An absolute ethical prohibition of placebo-controlled trials in psychiatric disorders for which standard, effective treatments exist is rejected because it is based on a flawed conception of research ethics, ignores important contextual factors characteristic of psychiatric research, and could lead to the approval and use of new medications that appear equivalent in efficacy to standard treatments but may be no more effective than placebos. Four standards governing the ethical use of placebos in psychiatric clinical trials are explicated: 1) placebo-controlled trials should have scientific and clinical merit; 2) risks should be minimized and justified by the anticipated benefits of generating clinically relevant scientific knowledge and the expected benefits, if any, to individual patient volunteers; 3) patient volunteers should give informed consent; and 4) investigators should offer short-term treatment optimization to patient volunteers after completion of research participation. Biol Psychiatry 2000;47:707–716

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Introduction

The ethics of using placebos in clinical trials has recently received increased attention and generated considerable controversy (Taubes 1995). Opponents of current practice in clinical research contend that use of placebo controls is always unethical when standard, proven treatment exists (Freedman et al 1996; Rothman

and Michels 1994). Defenders of current practice respond by arguing that placebo-controlled designs represent “the gold standard” for clinical trials of treatment efficacy (Clark and Leaverton 1994; Leber 1986; Rickels 1986) and that placebo arms of clinical trials are ethically acceptable provided that patients receiving placebo are not at risk for serious harm and give informed consent (Levine 1999). The debate has focused heavily on psychiatric research, owing to ethical concern about research involving potentially vulnerable, mentally ill patients and the frequency of placebo-controlled trials in this field despite the existence of standard, effective treatments.

In this article, I review ethical considerations relevant to this debate and endeavor to stake out a middle-ground position. I argue that an absolute ethical prohibition of placebo-controlled trials in psychiatric disorders for which standard, effective treatments exist is unsound for three major reasons. First, it is based on a flawed conception of research ethics, which inappropriately applies the normative framework of clinical medicine to clinical research. Second, it ignores important contextual factors characteristic of psychiatric research, including the limited efficacy and often-intolerable side effects of standard treatments and the high rates of placebo responses in clinical trials. Third, the alternative of active-controlled trials comparing experimental with standard drugs without placebo controls could lead to the approval and use of new medications that appear equivalent in efficacy to standard treatments but may be no more effective than placebo. Nevertheless, placebo-controlled trials are morally problematic and stand in need of justification when effective treatments are clinically available. Careful design and conduct of placebo-controlled trials are necessary to assure protection of patient volunteers.

What Makes Placebo-Controlled Trials Ethically Problematic?

Although widely considered to be the gold standard for testing treatment efficacy, placebo-controlled trials prompt ethical concern when patients in the placebo arm fail to receive standard, effective treatment. These patient volunteers are exposed to the risks of harm associated with

From the Intramural Research Program, National Institute of Mental Health and the Department of Clinical Bioethics, National Institutes of Health, Bethesda, Maryland.

Address reprint requests to Franklin G. Miller, Ph.D., NIH, Department of Clinical Bioethics, Clinical Center, Building 10, Room 1C118, Bethesda MD 20892-1156.

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untreated illness for the duration of their participation in the clinical trial. A consensus exists that placebo-controlled trials are unethical if patients risk death or irreversible serious morbidity as a result of having standard treatment withheld. Thus placebo-controlled trials in oncology are typically limited to testing the efficacy of "add-on" treatments combined with standard therapy. In contrast, ethical controversy surrounds placebo-controlled trials when withholding of standard treatment for research subjects randomized to placebo does not pose comparable risks of harm. Placebo-controlled trials in psychiatry fall squarely into this domain.

It is important to note that not all placebo-controlled trials pose special ethical problems. When no effective treatment exists for a given disorder, it is not ethically problematic to conduct a trial comparing placebo with an experimental agent or with a clinically available agent that has not been shown effective for this condition. In this case, patients in the placebo arm are not denied proven, effective treatment. Indeed, they may be better off than are those who receive the experimental treatment if it lacks efficacy or produces uncomfortable or harmful side effects. For similar reasons, trials testing experimental drugs against placebo in groups of treatment refractory patients are not considered ethically suspect because for these patients, standard treatment has proven ineffective. Many treatment refractory patients, however, have a partial response to standard medications or find them intolerable because of side effects. Enrolling such patients in placebo-controlled trials raises ethical concern insofar as they may experience symptom worsening on placebo. Treatment augmentation trials compare an "add on" experimental treatment with placebo among patient volunteers, all of whom also receive standard treatment. The design of these trials is ethically innocuous because patients are not asked to forego treatment of proven efficacy.

Placebo-controlled trials of maintenance treatment also raise ethical issues (Lieberman et al 1999). In trials of maintenance treatment, the principal research question under investigation concerns the clinical need for long-term drug treatment, which may also include the search for predictors of relapse. In this research design, patient volunteers who have responded positively to medication are randomly assigned in double-blind fashion to either continued treatment or placebo for a specified period of time. By their very nature, such trials require a placebo or no-treatment arm, but they are ethically problematic because of the risk of symptom worsening or relapse. This research design will not be considered further here; however, the guidelines presented below for the justification and use of placebo controls in efficacy trials are also relevant to maintenance trials.

Regulatory Standards and Codes of Ethics

Regulatory standards and codes of ethics differ in their guidance concerning placebo-controlled trials when standard, effective treatments exist. U.S. federal regulations governing human subjects research contain no explicit prohibition or restriction of the use of placebo controls in clinical trials (Code of Federal Regulations 1991). Research involving human subjects can be approved by Institutional Review Boards (IRBs) provided that several conditions are met, including the following: 1) "Risks to subjects are minimized . . . by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk"; 2) "risks to subjects are reasonable in relationship to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result"; and 3) "informed consent will be sought from each prospective subject or the subject's legally authorized representative" (45CFR 46.111).

Critics of placebo-controlled trials in psychiatry might argue that they should be prohibited under the federal regulations because they expose research subjects to unnecessary risks, but this would be disputed by those who see placebo-controlled trials as the scientific design of choice in this field and contend that the risks of withholding effective treatment during time-limited placebo trials are not severe for psychiatric patients. The fact that the federal regulations include the importance of scientific knowledge to be potentially gained from research within the scope of risk-benefit assessment suggests the justifiability of placebo-controlled trials. Nonetheless, the *Institutional Review Board Guidebook* prepared by the Office for Protection from Research Risks, which oversees human subjects research, declares that "A design involving a placebo control should not be used where there is a standard treatment that has been shown to be superior to placebo by convincing evidence" (Office for Protection from Research Risks 1993).

Regulations and guidelines of the U.S. Food and Drug Administration (FDA) directly address the use of placebo-controlled trials. They require "adequate and well-controlled" studies to demonstrate the effectiveness of drugs as a condition of approving their clinical use (Code of Federal Regulations 1985). Although the FDA does not require placebo controls, its policy gives a decided preference to placebo-controlled trials when risks of death or serious harm are not at stake. In defining an "adequate and well-controlled study," FDA regulations state that "The study uses a design that permits a valid comparison with a control to provide a quantitative assessment of drug effect." Among the variety of control conditions considered, placebo controls are mentioned first. Concerning

active treatment controls, the regulations state: "The test drug is compared with known effective therapy; for example, where the condition treated is such that administration of placebo or no treatment would be contrary to the interest of the patient."

It might be argued that FDA regulations should favor active-controlled trials whenever standard, effective treatment exists because use of placebo controls in this case is "contrary to the interest of the patient." Nonetheless, in a "Supplementary Advisory: Placebo-Controlled and Active Controlled Drug Study Designs" (United States Food and Drug Administration 1989), the FDA pointed out methodological limitations of active-controlled designs. Relevant to psychiatric research is the following statement from these guidelines: "For certain drug classes, such as analgesics, antidepressants or anti-anxiety drugs, failure to show superiority to placebo in a given study is common. . . . In those situations active control trials showing no difference between the new drug and control are of little value as primary evidence of effectiveness and the active control design, the study design most often proposed as an alternative to use of a placebo, is not credible."

The Declaration of Helsinki, endorsed by the World Medical Association, has been appealed to in support of the position that placebo-controlled trials are unethical in disorders for which treatments of proven efficacy exist (Rothman and Michels 1994). The relevant statement cited in favor of this ethical stance is the following: "In any medical study, every patient—including those of a control group, if any—should be assured of the best proven diagnostic and therapeutic method" (World Medical Association 1996). Critics of this ethical position have responded that the cited language would also appear to rule out any randomized clinical trial comparing a standard with an experimental treatment (Lasagna 1995; Levine 1999). The point of these trials is to determine if the experimental treatment is at least as effective as standard treatment. Patients randomized to experimental treatment are not assured "the best proven" treatment because the efficacy of the experimental treatment has yet to be determined and is the very issue under investigation in the trial.

The recently proposed draft revisions to the Declaration of Helsinki, which have occasioned considerable controversy, clearly permit wider use of placebo-controlled trials: "When the outcome measures are neither death nor disability, placebo or other no-treatment controls may be justified on the basis of their efficiency" (Brennan 1999). In contrast, Canada's new Tri-Council Policy Statement on Ethical Conduct for Research Involving Humans states: "The use of placebo controls in clinical trials is generally unacceptable when standard therapies or interventions are available for a particular patient population" (Weijer 1999).

The divergent guidance of regulations and codes of ethics indicates the need for ethical analysis to illuminate the moral considerations at stake in the controversy over placebo-controlled trials and arrive at an ethically sound position on this complex issue.

Rationale for Opposition to Placebo-Controlled Trials

Ethical opposition to placebo-controlled trials in situations where standard, effective treatments exist relies on appeal to a central norm of medical ethics: individualized, patient-centered beneficence. Physicians have an obligation to promote the benefit of patients suffering from illness by offering them medically indicated treatment. Correlatively, patients under the care of a physician have a right to medically indicated treatment. Patients randomized to a placebo arm of a clinical trial fail to receive standard, effective treatment for their condition, thus violating the moral obligation of physician-investigators and the rights of patient volunteers (Freedman et al 1996). According to this ethical perspective, the placebo-controlled trials to test the efficacy of new selective serotonin reuptake inhibitors in depressed patient volunteers and the "atypical" neuroleptics in patients with schizophrenia would be considered unethical, given the existence of the tricyclic antidepressants and standard neuroleptics, which have been proven effective.

In contrast, an active-controlled trial comparing an experimental treatment to a standard treatment would not be unethical, provided that reasonable doubt exists in the community of physician-investigators concerning the relative efficacy of the two treatments. This condition for ethical clinical trials is known as "clinical equipoise" (Freedman 1987). When clinical equipoise exists, patient volunteers are not randomized to a treatment known to be inferior to a clinically available treatment.

In addition to declaring the use of placebos in clinical trials unethical when treatments of proven efficacy are available, opponents of placebo-controlled trials in this situation argue that they lack clinical utility. When effective treatment exists for a given condition, clinical trials should compare experimental medications with standard treatment rather than with placebo. Instead of seeking to determine whether the experimental treatment "is better than nothing," clinical trials should test whether it is superior or equivalent in efficacy to standard treatment that has been proven effective (Rothman and Michels 1994; Weijer 1999).

Methodological Considerations

Before offering a critique of the ethical opposition to placebo-controlled trials and suggesting an alternative

ethical framework, I will examine the claim that active-controlled trials have greater scientific and clinical value than placebo-controlled trials when standard, effective treatments exist for the condition under investigation. Two key methodological considerations are relevant to assessing the validity of this claim.

First, the often-repeated assertion by critics of placebo-controlled trials that they test whether experimental drugs "are better than nothing" flies in the face of extensive evidence for the power of the placebo response, particularly in psychiatry (Shapiro and Shapiro 1997). Psychiatric research has demonstrated high rates of placebo responses (from 25% to 50% or more) across a range of psychiatric diagnoses, including panic disorder, depression, and schizophrenia (Addington 1995; Brown 1988; Hirschfeld 1996). Indeed, whether antidepressant medications have specific therapeutic potency beyond the placebo response has been questioned (Greenberg and Fisher 1997). One psychiatric investigator has recommended 4 to 6 weeks of placebo treatment (without deception) for a substantial proportion of depressed patients (Brown 1994). Although the nature of the placebo response remains poorly understood, a variety of factors may contribute to producing positive responses among research subjects receiving placebo, including the expectation of benefit from participating in clinical trials, the therapeutic milieu of the research environment, and the clinician-patient relationship (Shapiro and Shapiro 1997). Because substantial proportions of patient volunteers who receive placebos in psychiatric clinical trials show clinically significant improvement, demonstrating superiority to placebo represents a demanding test of efficacy for experimental drugs or procedures.

Second, active-controlled trial designs, comparing experimental with standard treatment, have potentially serious methodological limitations (Makuch and Johnson 1989; Temple 1997). Such studies can produce meaningful results when they are designed to test whether experimental drugs prove significantly superior to standard medication. In psychiatry, however, new drugs for a mental disorder are typically no more effective on the whole than standard treatment but may have clinical value because they have less severe side effects or work better in some patients. Accordingly, demonstrating equivalence between a novel and a standard drug can be useful, provided that the novel drug is better than placebo. Nonetheless, active-controlled trials designed to test the equivalence of experimental and standard treatment may produce misleading results. If the experimental treatment in such a clinical trial is demonstrated to be equivalent to the standard treatment, it does not follow that the experimental treatment is more effective than placebo; it is possible that in this particular trial, the standard treatment—which has previously been shown to be superior to placebo—is in fact not more

effective than placebo. A variety of factors might explain this seemingly anomalous result, including a high rate of placebo response in the study population, fluctuating symptoms of illness, and spontaneous remission. Such factors are likely to be operative in psychiatric disorders. Without a placebo control arm, it is impossible to determine reliably whether an experimental drug that is demonstrated to be as effective as standard treatment is actually superior to placebo.

That this is not merely a theoretical concern is demonstrated by Temple (1997), who analyzed the data from six studies of an experimental antidepressant presented in a marketing application to the FDA. These studies compared the experimental drug to a standard antidepressant (imipramine) and placebo. In all six trials, a substantial and nearly identical reduction in depressive symptoms was associated with both the experimental and standard treatment. In five of the six trials, however, no significant difference was found between either the experimental or standard drug and placebo in terms of reduction in symptoms of depression. The one trial showing superiority of the active treatments to placebo was a very small study consisting in total of only 22 patients in the three study arms. Without placebo controls, the experimental drug would have appeared worthy of approval because it proved as effective as imipramine. In fact, neither the standard nor the experimental drug was more effective than placebo in this group of 392 study subjects.

Owing to the methodological limitations of active-controlled study designs, a policy of prohibiting placebo-controlled trials when proven effective treatment exists could have potentially serious consequences. Active-controlled studies showing the equivalence of experimental and standard drugs, in the absence of placebo controls, could lead to the approval of new drugs that are no better than placebo (Temple 1997). On the other hand, if demonstrating superiority to standard treatments were required for approval of new drugs, this would call for much larger sample sizes than are needed for placebo-controlled trials. It is likely that such a policy would expose many more patient volunteers to experimental drugs that may prove ineffective or have intolerable side effects, as well as add significant cost and delay to the process of drug development (Zipursky and Darby 1999).

Smaller two-arm trials comparing experimental drugs with placebo are useful in the early stage of efficacy testing. Once experimental drugs, or clinically available drugs that have not been tested for a given indication, have proved superior to placebo, a three-way trial design comparing a promising experimental drug, standard drug, and placebo can be especially valuable (Leber 1986). Clinical trials comparing a novel treatment with a standard treatment and placebo combine the scientific rigor of

placebo-controlled trials with the potential clinical utility of testing an experimental agent against an existing standard therapy.

Ethical Critique

Regardless of these methodological and consequentialist considerations, if placebo-controlled trials involving patients for whom standard, effective treatments exist are unethical, then other ways of testing treatment efficacy should be adopted. The ethical opposition to the use of placebos in clinical trials is based on the norm of medical ethics that physicians have an obligation to promote benefit to individual patients by providing optimal medical care. Although it may seem natural that the norm of individual, patient-centered beneficence should also govern clinical research, this stance ignores significant differences between clinical research and clinical medicine. Because clinical research aims at producing generalizable knowledge concerning the understanding and treatment of disease, ethical standards for clinical research are not identical to those governing the practice of clinical medicine.

If individualized beneficence were the primary standard for clinical research, then any research interventions posing risks to patient volunteers not justified by compensating medical benefits would be ethically prohibited. Nonetheless, patient volunteers enrolled in clinical research routinely receive nontherapeutic research interventions that are not medically indicated and that pose risks. For example, psychiatric research commonly uses positron emission tomography (PET) scans and lumbar punctures to investigate the pathophysiology of psychiatric disorders. PET scans carry the risks of radiation exposure and complications from inserting arterial lines, and lumbar punctures may cause persistent headaches. A standard of individualized beneficence that rules out placebo-controlled trials when effective treatments exist would also prohibit such nontherapeutic investigational procedures. It follows that clinical research would be significantly curtailed if investigators were held to the same standard of individualized beneficence that applies to clinical medicine.

If clinical research is regarded as continuous with, or an extension of, clinical medicine, then patients suffering from illness should not receive placebos in clinical trials when standard, effective treatments exist, for this is to provide medical care known to be inferior. Because the physician-investigator is not operating primarily in the role of the patient volunteer's doctor in the context of clinical trials, however, it is not clear that the standard of therapeutic fidelity to individual patients, characteristic of clinical medicine, must govern placebo-controlled trials.

Clinical trials are concerned with treatment responses in groups of patients representing the class of patients with a given condition. This scientific orientation toward groups of patients and critical features of study design, such as randomization and blinding, make clinical trials radically different from standard clinical medicine. Consequently, the ethical argument against the use of placebos in clinical research, based on the normative framework of clinical medicine, is open to question. Nonetheless, the potential for confusion and conflict between physician and investigator roles in clinical research makes it imperative that both the physician-investigator and the patient volunteer clearly understand and appreciate the differences between clinical trials and treatment in routine clinical practice (Miller et al 1998).

Beneficence is a basic principle of the ethics of clinical research, but it differs in scope from beneficence in clinical medicine. Unlike clinical medicine, clinical research is concerned primarily with benefits to future patients and society from generating biomedical knowledge. In clinical medicine, anticipated benefits to the individual patient justify risks of diagnostic and treatment interventions. Research risks are justified primarily by anticipated benefits of generating scientific knowledge and secondarily by benefits, if any, to individual subjects.

Investigators do have moral obligations to individual patient volunteers to protect them from harm and to promote their well-being consistent with the goal of pursuing scientific knowledge. Patient volunteers should not be subjected to risks of irreversible harm as a result of research participation. Insofar as withholding potentially effective treatment in placebo-controlled trials exposes patient volunteers to less serious risks of clinical deterioration and symptomatic distress, such studies are morally problematic. Are such studies necessarily unethical? I contend that time-limited periods of treatment withholding in placebo-controlled trials of new psychiatric treatments may be ethically justifiable, provided that the design and conduct of these studies satisfy stringent ethical standards and guidelines.

What Ethical Standards Should Govern Placebo Use in Clinical Trials?

Four ethical standards must be satisfied to legitimate the use of placebo controls in clinical research: 1) placebo-controlled trials should have scientific and clinical merit; 2) risks should be minimized and justified by the anticipated benefits of generating clinically relevant scientific knowledge and the expected benefits, if any, to individual research subjects; 3) patient volunteers should give informed consent; and 4) investigators should offer short-

term individualized treatment optimization to patient volunteers after completion of research participation.

Scientific Merit

As in all clinical research, the justification for exposing patient volunteers to the risks of placebo-controlled trials depends on the scientific merit and potential clinical utility of these studies. Because placebo-controlled trials generally require smaller sample sizes than active-controlled trials, this research design may be advocated for reasons other than scientific or clinical merit. Specifically, placebo-controlled trials are convenient to serve the commercial interests of pharmaceutical companies in obtaining approval for marketing new drugs and the professional interests of investigators in completing "successful" studies. To protect patient volunteers and promote research that is scientifically sound and clinically useful, IRBs should require that scientific protocols for placebo-controlled trials demonstrate rigorously why placebo controls are necessary or desirable.

Risk-Benefit Assessment

Risk-benefit assessment applies the principles of nonmaleficence and beneficence to clinical research (Beauchamp and Childress 1994; The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research 1978). The acceptability of placebo controls in clinical research depends on both the degree of risks posed to patient volunteers from temporary withholding of treatment and the efficacy and side-effect profile of current treatments. As the magnitude and probability of lasting harm or temporary distress associated with withholding treatment increases, the use of placebos becomes more problematic and difficult to justify. Also relevant is the quality of standard treatments. If clinically available drugs are highly effective in curing or preventing serious disease without producing intolerable side effects then it is difficult to justify placebo-controlled trials for new treatments for this condition; however, if current treatments have limited efficacy, produce uncomfortable side effects, or both, then placebo-controlled trials are easier to justify.

Several contextual features of psychiatric research are relevant to the justifiability of placebo-controlled trials (Lieberman 1996). Psychiatric disorders are chronic, fluctuating conditions that produce substantial morbidity but usually are not life-threatening. Nonetheless, patients suffering from psychiatric disorders are at considerably increased risk of suicide. A review of suicidality in clinical trials of drugs for treatment of depression found significantly greater suicidal ideation in patients on placebo compared with those on antidepressants in some studies

but no significant differences in suicide (Mann et al 1993). Standard psychiatric treatments provide partial relief of symptoms for many, but not all patients; they are not curative or fully preventive. Existing treatments have significant side effects, which many patients find intolerable. Finally, as noted above, psychiatric clinical trials have demonstrated high rates of placebo response.

In view of these factors, patient volunteers randomized to placebo in short-term psychiatric clinical trials are not likely to be greatly disadvantaged on the whole compared with those who receive experimental or standard treatment. Although patient volunteers on placebo arms of clinical trials testing the efficacy of drugs for the treatment of depression, schizophrenia, and other psychiatric disorders may experience symptomatic worsening, there is no evidence that short-term periods on placebo in psychiatric research produce any lasting harm (Addington 1995; Quitkin 1999). Nevertheless, psychic distress experienced by patient volunteers receiving placebos is a matter of moral concern and can be tolerated ethically only if it does not become severe. For some groups of seriously ill patients, the risks of being off medications in placebo-controlled trials may be sufficiently great to preclude their enrollment (Prien 1988).

Careful screening of prospective patient volunteers is required to minimize risks (Carpenter et al 1997). It is likely that many, if not most, patients interested in clinical trials will have experienced less than satisfactory response to standard treatment. Nonetheless, patients who have responded well to standard psychiatric medications should not be invited to participate in placebo-controlled trials (Streiner 1999), with the exception of studies of maintenance treatment. Patients known to be at substantial risk of suicide or a danger to others should be excluded. Prospective patient volunteers should be encouraged to consult with their physicians before deciding whether to enroll in a placebo-controlled trial (Levine 1986, 111-112). For those who lack a physician, consultation with a clinician not involved in the research project is desirable.

The duration of the placebo period should be limited to the shortest time required for adequate efficacy testing. During the conduct of the clinical trial, monitoring procedures are necessary to protect patient volunteers (Quitkin 1999). For severely ill patients, consideration should be given to limiting placebo-controlled trials to inpatient settings with constant monitoring and the ready availability of "rescue" medications in case of significant deterioration. In outpatient trials, investigators should maintain frequent contact with patient volunteers to assess symptomatic worsening and intervene appropriately. Consideration should be given to requiring research protocols to specify criteria for removing patient volunteers from clinical trials owing to symptom severity. In any case,

clinical judgment will be necessary, and investigators should err on the side of patient safety.

Informed Consent

The purpose of informed consent is to promote and respect the self-determination of research subjects. As the term “informed consent” suggests, patient volunteers must understand what is involved in enrolling in a particular clinical trial and authorize research participation by means of voluntary agreement. Because psychiatric research studies disorders of the brain, concern and controversy has arisen over whether psychiatric patients are capable of giving informed consent to research participation (Berg and Appelbaum 1999; Capron 1999; Elliot 1997; National Bioethics Advisory Commission 1998). The debate has also focused on mechanisms of assessing decision-making capacity before enrollment of patient volunteers in psychiatric research (Miller and Rosenstein 1999). These complex issues are not addressed here.

Enrollment in placebo-controlled trials of individuals who are not capable of giving informed consent should be permitted only under strictly limited circumstances. Placebo controls should be understood as a nontherapeutic feature of research design (Levine 1986, 203–206). Use of placebos may pose greater than minimal risk, especially when it involves withholding standard, effective treatment for a condition associated with considerable morbidity. Accordingly, patients with severely impaired decision-making capacity should not be enrolled in placebo-controlled trials when eligible subjects capable of giving informed consent are available. Some clinical trials, however, may be designed to test the efficacy of treatments in severely ill psychiatric patients who are likely to have impaired capacity. As a rule, incapacitated subjects may be enrolled in placebo-controlled trials only when their enrollment is necessary to conduct scientifically sound and clinically promising studies. These subjects should either have advance directives authorizing such research participation or be enrolled with the informed consent of authorized surrogate decision makers.

The adequacy of informed consent in the current practice of clinical research is open to question. In empirical studies of the informed consent process in psychiatric research, Appelbaum and his colleagues have found deficiencies in the understanding and appreciation of patient volunteers regarding their participation in clinical trials (Appelbaum et al 1987). For example, “With regard to nontreatment control groups and placebos, fourteen of thirty-three (44 percent) subjects failed to recognize that some patients who desired treatment would not receive it.” In general, interviewed subjects tended to view their participation in clinical trials as intended to promote their

own individual benefit. Appelbaum et al described this phenomenon, which many observers believe to be pervasive in clinical research, as “the therapeutic misconception.”

Elements of informed consent do not differ essentially in placebo-controlled trials from other forms of clinical research. Some points, however, deserve emphasis. It is imperative that patient volunteers understand the nature of the study under consideration and how it differs from standard clinical practice, the rationale for placebo use, random assignment, the probability of receiving a placebo, blinding of patient volunteers and investigators, and so forth. Among the risks that must be disclosed and understood are lack of improvement that patient volunteers randomized to placebo might have experienced if they had received standard or experimental treatment and symptomatic worsening during the placebo phase. Patient volunteers should be warned that they may experience suicidal ideation and that, if so, they should report this to the investigators. Prospective subjects need to be made aware of alternatives to research participation. Specifically, they should be informed about the clinical availability of standard, effective treatments for their condition.

Patients must be free of coercion or undue inducement to enroll in clinical trials. They should be informed that they have a right to withdraw without penalty from research participation at any time. Investigators may encourage patient volunteers to remain enrolled in clinical trials but must honor their decisions to withdraw, regardless of doubts about their decision-making capacity. Severely ill patient volunteers are at risk of losing awareness of their right to withdraw from research. Family members or designated surrogate decision makers should be encouraged to monitor their condition and empowered to decide on their behalf to withdraw them from research if they deteriorate clinically to the point of losing decision-making capacity.

Treatment Optimization

Patient volunteers in placebo-controlled trials accept risks of research interventions and forego potentially effective treatment for the sake of contributing to scientific knowledge. Accordingly, they are owed the prospect of individualized therapeutic benefit in return. Placebo-controlled trials should be accompanied by a short-term treatment optimization phase in which physician-investigators endeavor to help patient volunteers, at no cost to them, find the best available treatment for their condition and undertake discharge planning for continuing clinical care. This provision is based on principles of nonabandonment, reciprocity, and just compensation. To avoid abandoning patient volunteers, investigators must provide clinical

stabilization and referral for needed treatment at the conclusion of research participation. Beyond this minimal commitment, a time-limited period of treatment optimization functions as an important and ethically appropriate quid pro quo for research participation (Miller et al 1998). In addition, patients whose symptoms have worsened during the clinical trial should be entitled to individualized treatment aimed at making them at least as well as they were before enrollment in research.

The obligation to provide treatment optimization should include patient volunteers who drop out of the clinical trial because of intolerable symptomatic worsening or side effects, as well as those who complete the study. The duration of treatment optimization may vary with respect to various psychiatric disorders and the clinical situation of particular patients. It should be clearly understood by patient volunteers as a short-term commitment so as not to provide undue inducement for research participation.

Public Justification

Exposure of patient volunteers to risks to test the efficacy of new treatments places a burden on investigators to justify the use of placebos in clinical research. In addition to justifying placebo-controlled trials in the context of IRB review and approval of scientific protocols, investigators should be required to address pertinent ethical issues associated with this research design in scientific articles published in professional journals (Charney et al 1999; Miller et al 1999). Currently, such articles in the psychiatric research literature rarely go beyond stating that the research was approved by an IRB and that informed consent was obtained. A requirement that investigators in scientific articles justify the rationale for the use of placebos—especially when standard, effective treatment exists—and discuss protections to minimize risks to subjects provides an additional safeguard for the ethical conduct of clinical research. Peer reviewers should scrutinize carefully the way in which ethical issues are addressed, just as they examine critically the discussion of methodological issues. Additionally, journal editors should consider seeking ethical commentary for articles reporting research that raise ethical issues. In view of the climate of distrust generated by reports in the news media alleging abuses in the conduct of psychiatric research (Hilts 1998; Whitaker and Kong 1998), including the use of placebos (Kong 1999), more detailed attention to ethical issues in the scientific literature might help improve the public perception of psychiatric research.

Conclusion

Critics of placebo-controlled trials have contended that they are unethical whenever their use would result in withholding standard, effective treatment that has a rea-

sonable prospect of benefiting patient volunteers. In a critique of this stance, I have argued that it appeals to a standard of individual, patient-centered beneficence that, if strictly applied, would make it impossible to conduct any clinical research employing nontherapeutic interventions that pose risks to patient volunteers. Moreover, the alternative of active-controlled trials—proposed as superior ethically and more useful clinically than placebo-controlled trials when standard, effective treatment exists—is subject to serious methodological weaknesses and might lead to validating new treatments that may be no more effective than placebo.

The ethical criticism of placebo-controlled trials, however, has merit in drawing attention to the need for ethical scrutiny and justification of studies using this research design. I have presented an alternative bioethical perspective that regards placebo-controlled trials in psychiatric research as ethically defensible provided that these studies have scientific merit; the risks are reduced to an acceptable minimum and justified by the anticipated benefits of producing biomedical knowledge; patient volunteers give adequate informed consent; and investigators offer short-term treatment optimization to patient volunteers at the conclusion of research participation. Empirical research is needed to determine whether current practice of psychiatric clinical trials conforms to these ethical standards and to suggest ways to improve the protection of patient volunteers.

The ethical justification of placebo-controlled trials in psychiatric research depends critically on the contextual circumstances defining the nature and current treatment of psychiatric disorders. If scientific progress leads to the development of psychiatric medications that are highly effective with minimal side effects, placebo-controlled trials that withhold such treatment will become more difficult to justify. In that case, the use of placebo-controlled trials will have helped produce improvements in treatment that obviate the need and rationale for continued use of this research design.

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